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<p>(21) International Application Number: PCT/US93/11209</p> <p>(22) International Filing Date: 18 November 1993 (18.11.93)</p> <p>(30) Priority Data: PL 6074 27 November 1992 (27.11.92) AU 07/995,501 22 December 1992 (22.12.92) US</p> <p>(71) Applicant: NAPRO BIOTHERAPEUTICS, INC. [US/US]; 2885 Wilderness Place, 46B, Suite 200, Boulder, CO 80301 (US).</p> <p>(72) Inventors: CARVER, David, R.; 4620 Starboard Drive, Boulder, CO 80302 (US). PROUT, Timothy, R.; 2227 Canyon Boulevard, #158, Boulder, CO 80302 (US). EWALD, Hernita; 300 E. 17th Avenue, #920, Denver, CO 80203 (US). ELLIOTT, Robyn; 12 Linererea Glade, Lanctwarrin, VIC 3910 (AU). HANDRECK, Paul; 26 Iris Road, Glen Iris, VIC (AU).</p> <p>(74) Agents: MARTIN, Timothy, J. et al.; 9250 W. 5th Avenue, Suite 200, Lakewood, CO 80226 (US).</p>	<p>(81) Designated States: BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BI, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: INJECTABLE COMPOSITION</p> <p>(57) Abstract</p> <p>A composition of taxol and polyethoxylated castor oil is pH balanced to have a pH less than 8.1 to improve stability. This composition can include an acid, preferably citric acid, to adjust the pH value. The invention includes a method of formulating a taxol solution for injection by mixing an acid with a carrier material, such as castor oil, to form a carrier solution after which taxol is mixed with the carrier solution to form the taxol solution at a pH of less than 8.1. The method may include the step of slurrying the taxol in alcohol before mixing with the carrier solution.</p>		

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INJECTABLE COMPOSITION

This invention relates to a solution of taxol having improved stability.

BACKGROUND OF THE INVENTION

Taxol is a compound extracted from the bark of a western yew, Taxus brevifolia and known for its antineoplastic activity. It is described for example in The Merck Index, Eleventh Edition 1989, monograph 9049.

In 1977, taxol was chosen for development as an antineoplastic agent because of its unique mechanism of action and good cytotoxic activity against IP implanted D16 melanoma and the human X-1 mammary tumor xenograft.

Taxol is believed to function as a mitotic spindle poison and as a potent inhibitor of cell replication in vitro. Other mitotic spindle points (colchicine and podophyllotoxin) inhibit microtubule assembly. Taxol employs a different mechanism of action since it appears to shift the equilibrium of polymerization/depolymerization toward polymer assembly and to stabilize microtubules against depolymerization under conditions which would cause rapid disaggregation of microtubules. The interference with the polymerization/depolymerization cycle in cells appears to interfere with both the replication and migration of cells.

After extensive preclinical screening in mouse tumor models, taxol entered clinical trials in 1983. Over the past few years, taxol has demonstrated good response rates in treating both ovarian and breast cancer patients who were not benefiting from vinca alkaloid or cisplatin therapy. It has also shown encouraging results in patients with other types of cancer including lung, melanoma, lymphoma, head and neck.

For further information, reference may be made to the U.S. National Cancer Institute's Clinical Brochure for Taxol, revised July 1991, and papers presented at the Second National Cancer Institute Workshop on Taxol and Taxus held in Alexandria, Virginia USA on September 23-24, 1992.

BRIEF DESCRIPTION OF THE INVENTION

It is a disadvantage of the known formulation that the

taxol therein degrades, with the result that the shelf life of the formulation is unsatisfactory, and there is therefore a need for a taxol solution of improved stability.

Accordingly, in a general aspect the invention provides a solution containing taxol, cremophor EL TM and ethanol, characterized in that the pH of the solution has been adjusted into the range 1 to 8 by addition of an acid. Acids in the form of powders, for example citric acid, are preferred over those which contain water, for example sulfuric acid. The most preferred acid for use in accordance with the present invention is citric acid but a wide range of acids may be used including the following:

- Citric acid - monohydrous
- Citric acid - anhydrous
- Citric acid - hydrous
- Acetic acid
- Formic acid
- Ascorbic acid
- Aspartic acid
- Benzene sulphononic acid
- Benzoic acid
- Hydrochloric acid
- Sulphuric acid
- Phosphoric acid
- Nitric acid
- Tartaric acid
- Diatrizoic acid
- Glutamic acid
- Lactic acid
- Maleic acid
- Succinic acid

DETAILED DESCRIPTION OF THE INVENTION

Due to its limited solubility in water, Taxol is usually prepared and administered in a vehicle containing cremophor EL TM (a polyethoxylated castor oil which acts as a solubilizer) and ethanol. A commercially available solution supplied by

Bristol-Myers Squibb (BMS) is formulated with these components and has a pH of 9.1.

As indicated above, the invention essentially teaches addition of an acid to a taxol formulation to adjust its pH into the range 1 to 8, preferable 5 to 7.

In a preferred procedure adopted by the applicant, which it will be clearly understood is non-limiting, the following steps were carried out:

Mixing Instructions

SOLUTION 1

Citric acid was dissolved in absolute alcohol, using a ratio of 8 mls of absolute alcohol to 1 gram of citric acid, and the solution was stirred for fifteen (15) minutes.

SOLUTION 2

Cremophor EL was weighed out into the main mixing vessel.

SOLUTION 3

Solution 1 was added to solution 2, and the container used for solution 2 was washed with a minimum quantity of absolute alcohol to ensure complete transfer of the citric acid. Solution 3 was mixed and bubbled with nitrogen for at least 15 minutes. The taxol was weighed out and slurried using absolute alcohol, using a ratio of 8 ml of absolute alcohol to 1 gm of taxol. The slurried taxol was added to solution 3 and the slurrying vessel was washed with a minimum quantity of absolute alcohol. Solution 3 was adjusted to 75% of required volume using absolute alcohol, and thoroughly stirred for at least 45 minutes until completely dissolved. Once completely dissolved, the volume was checked and made up as necessary with absolute alcohol and the final solution stirred for 5 minutes.

Example 1

A solution was prepared with the following formulation:

Formulation: (Sample 1)

Cremophor EL	0.5 mL
Citric Acid (Anhydrous)	2.0 mg
Taxol	6.0 mg
Absolute Alcohol to	1.0 mL

The pH of this solution was determined as 6.1.

The stability of this sample was compared with a sample prepared by the formulation stated in the NCI Taxol Clinical brochure (as follows) which had a pH of 9.1. (Sample 2)

<u>Sample 2</u>	<u>per mL</u>
Taxol	6 mg
Cremophor EL	0.5 mL
Absolute Alcohol	to 1 mL

The solutions were filled into clear type 1 glass 5 mL vials and sealed with rubber bungs.

The solutions were stored at 40°C for 7 (seven) days and the stability results are shown in Table 1.

	<u>Sample 1</u>	<u>Sample 2</u>
pH	6.2	9.0
Potency	96.6	86.7
Major individual	0.3%	5.1% impurity
Total impurities	2.0%	12.2%

Clearly Sample 1 showed significantly increased stability over Sample 2.

Example 2

A solution was prepared with the following formulation:

Formulation: (Sample 3)

Cremophor EL	0.5 mL
Taxol	6.0 mg
Absolute Ethanol	to 1 mL

pH adjusted to 6.6 with 1.0M Acetic Acid.

The solution was filled into clear type I glass 5 mL vials and sealed with rubber bungs.

The solution was stored at 40°C for 7 days.

The stability results obtained are compared to those seen with Sample 2.

	<u>Sample 3</u>	<u>Sample 2</u>
pH	6.7	9.0
Potency	97.5	86.7
Major individual	0.3%	5.1% impurity

Total impurities 2.3% 12.2%

Again the significantly superior stability of the formulation according to the invention (Sample 3) is evident.

It will be clearly understood that the invention in its general aspects is not limited to the specific details referred to hereinabove.

We claim:

1. A composition comprising taxol in a polyethoxylated castor oil wherein said composition has a pH less than 8.1.

2. A method of formulating a taxol solution for injection in which the taxol does not readily degrade, comprising the following steps:

mixing acid with a carrier material to form a first carrier solution; and

mixing taxol with the first carrier solution to form a taxol solution having a pH of less than 8.1 whereby the taxol in the taxol solution does not readily degrade.

3. A method according to claim 2 wherein said acid is acetic acid.

4. A method according to claim 2 wherein said acid is citric acid.

5. A method according to claim 2 wherein said carrier material is polyethoxylated castor oil.

6. A method according to claim 2 including the step of slurring said taxol in alcohol before mixing said taxol with the first carrier solution.

7. A composite comprising:

taxol;

castor oil; and

anhydrous citric acid in sufficient amounts to adjust the pH of the composition to less than 8.1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/11209

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A01N 43/02

US CL :514/449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: "TAXOL?"; "COMPOSITION?"; "STAB?"; "PH"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,960,790 (Stella et al) 02 December 1990, See column 1, lines 61-65.	1-7
A	US, A, 4,942,184 (Hangwitz et al) 17 July 1990, see entire reference.	1-7
A	US, A, 5,157,049 (Hangwitz et al) 20 October 1982, see entire reference.	1-7
A	US, A, 4,814,470 (Colin et al) 21 March 1989, see entire reference.	1-7
T	US, A, 5,254,580 (Chen et al) 19 October 1993, see entire reference.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.^a Special categories of cited documents:

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